

Chronobiology perspectives in psychiatry

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ABSTRACT

The impairment of biological cycles – of the circadian cycle, especially – is the underlying cause of numerous organic and mental pathologies, by determining or worsening affective disorders, such as the hypnic ones. The development of chronotherapeutics that modulate the activity of synchronizing agents of the central nervous system, such as light and melatonin, represent an innovating alternative – with an almost ideal safety profile – to classic pharmacological therapies; however, the field is still perfectible and open to research.

KEYWORDS

chronotherapy, chronobiology, *zeitgeber*, affective disorders, hypnic disturbances

INTRODUCTION

Chronobiology is the science that studies the circadian, monthly and seasonal rhythms; it has developed exponentially in the past decade and it has recorded discoveries at the major molecular and neuroanatomic level. Circadian rhythm manifests itself at each hierarchical level: from the general population (e.g., most traffic accidents occur at night) to the individual (sleep/wake cycle), to every organ, cell and molecule. Changes in rhythm provide the temporal organization necessary for the right function at the right time (1, 2).

Biological rhythm is no a new notion for psychiatry; as early as the 19th century, more and more data have proven the importance of periodicity in psychopathology. In the '60s, Menninger-Lerchenthal proposed a hypothalamic neuroendocrine mechanism – to explain the astonishing precision of circadian and seasonal rhythms in close connection with clinical symptoms and behaviour – confirmed and detailed by numerous modern studies (1, 2).

The main synchronizing agent or *zeitgeber* for the central nervous system is light transmitted directly from the retina via the retinohypothalamic tract. The photic input to the central nervous system is nonvisual; thus, classic cone and rod photoreceptors – important for vision of colour, movement, shape and edges – play a secondary role to circadian photoreceptors at the level of retinal ganglion cells. They contain the photopigment melanopsin, which is sensitive to blue light. One important pathway from the central nervous system leads to the pineal gland, where melatonin is synthesized at night. The secretion of this hormone is inhibited by light (4, 9).

The main characteristic of a *zeitgeber* is that it can alter the direction of circadian rhythms, depending on the time of day. Both light and melatonin are *zeitgebers*. Favouring factors for oscillations of the circadian rhythm are found

in every organ and in every cell. Moreover, each organ has its own *zeitgeber*. Adequate temporal organization is crucial for coordinating functions that occur at the same time and for separating antagonistic functions (1).

Therefore, the clocks of both, brain and body are dependent on daily exposure to specific *zeitgebers*, for a good coordination. The desynchronization of the circadian rhythm perpetuates and exacerbates clinical symptoms and it can even cause psychopathology.

The study conducted by Bromundt on patients with schizophrenia found that the cognitive functioning of these patients depends on the degree of consolidated circadian rhythms.

At the same time, biological clocks are influenced by nonphotic *zeitgebers*, such as physical exercise, sleep and food (3). Social factors, such as jobs and other such demands, act indirectly on the central nervous system, because they determine the timing of meals, sleep, physical exercise and light exposure. They have been considered as therapeutic options (1, 4, 5).

Biological rhythms and affective disorders

Periodicity has an important role in the evolution of affective disorders; illness recurrence ranges from seasonal depressive episodes to rapid-cycling manic/depressive episodes. The symptoms related to diurnal and early morning variations of mood suggest rhythmic dysfunction. Circadian rhythms – including hormonal secretion, neurotransmitter function and body temperature – are impaired. Furthermore, hypnic disturbances represent another core element of bipolar disorder, and insomnia often predicts the onset of mood disorder symptomatology (1, 4, 5). At the same time, sleep disturbances are frequent residual symptoms of depression, thus marking an increased risk of relapse. Any disturbance of sleep and circadian rhythms brings along the risk of mood fluctuation, especially in individuals prone to it (6, 7).

Chronotherapy

The biological rhythms of each individual are vulnerable, and their misalignment entangles mood and sleep variations; the last two are closely connected. A series of methods based on light exposure /deprivation and on the modulation of *zeitgeber* in the central nervous system were created, all meant to resynchronize internal clocks.

These therapies – almost all involving no drugs – targeting the *zeitgebers* in the central nervous system are *chronotherapies*. They take various forms, adapted to the nature of mental symptomatology: light therapy, dark therapy, and sleep restriction therapy (1, 2, 28).

Light therapy

The first studies on seasonal affective disorder were initiated three decades ago (8). As it debuted under the influence of environmental triggers like shortened days, the light stimulating a summer day seemed the logical treatment – and it worked, eventually.

Light therapy was the first successful treatment in psychiatry based on neurobiological principles. It is currently the treatment of choice for seasonal affective disorders (9). Light is also an efficient „antidepressant” in nonseasonal depression (10, 11). Studies have found that light potentiates the effect of antidepressants in unipolar depression and of lithium in bipolar depression (1, 10, 11).

Light therapy is a viable alternative for patients who refuse or cannot tolerate psychotropic medication, as well as for *ante partum* depression. This form of therapy has been proven successful even for patients with chronic depression (two years or more) and for geriatric patients with hyperthymic negative symptomatology. Light therapy has also been used successfully in other psychiatric and neurological illnesses, including bulimia nervosa, childhood and adult

ADHD, Parkinson’s disease and Alzheimer dementia (13, 14).

In sleep medicine, light is used as *zeitgeber* to resynchronize the sleep schedule. The light box is the standard, most tested and used device in light therapy: it comprises a diffusion screen with a UV filter and 10,000 lux, at a distance of approximately 30 – 35 centimetres (recommended distance) (1, 9). Long-term exposure to wavelengths between 400 and 500 nm may induce photochemical retinal injury or it can precipitate age-related macular degeneration. Hence, the light box uses white illumination, with wavelengths lower than 450 nm (15). Though the circadian photoreceptors are more sensitive to lower wavelengths, there are no long-term safety or efficiency studies to allow blue light devices for the time being. In the treatment of seasonal affective disorders, the timing of light therapy is fundamental. It must be individually defined, considering the personal particularities of the internal body clock and of the sleep – wake cycles. The patients’ sleeping habits provide an indirect estimate of internal body clocks.

The Horne – Ostberg Morningness – Eveningness Questionnaire can be used to choose the best time to begin light therapy. It comprises 19 questions concerning the daily sleeping – waking patterns (12).

The side effects of this kind of therapy are rare; they include hypomania in patients with bipolar depression, mild visual complaints, irritability, headache and nausea, which usually disappear within a few days of treatment (9). Sleep disturbances may emerge that are usually associated with bad timing for light therapy (e.g., light therapy administered in the evening can determine difficulties in falling asleep and light therapy administered in the morning may lead to premature waking).

Dawn simulation is a more recent alternative to the light box, which involves a stimulation

with medium intensity signal that gradually increases over 45 minutes, from about 0.001 lux to approximately 300 lux during the last period of the sleep episode (up to two hours before awakening). This technique shortens the time spent by the patient considering that the patient, sleeps the entire time, but the effectiveness of dawn simulation is still an open matter (1, 27, 28).

Light therapy is often prescribed for the aforementioned pathology, especially for seasonal affective disorder (1).

Wake Therapy/Sleep Restriction

The slow response to most antidepressants is a major issue when it comes to treating patients with depression. In contrast, there is the paradoxical effect of sleep deprivation for one night and the following day. This form of therapy was first studied four decades ago. Approximately 60 % of the patients respond with significant improvement of depressive symptomatology (13). The therapeutic effects are noticeable mostly when the patient is sleep deprived in the second half of the night (after 1 a.m.). When it is associated with light therapy and/or pharmacological therapies, it has been proven more effective and inducing long-term remission. It has proven effective in both bipolar and unipolar depression (16, 17). Sleep deprivation therapy includes 1 – 3 cycles of complete sleep deprivation separated by nights destined for recovery sleep. It has been shown that most patients can undergo various easy activities and even moderately complex activities (chores, on-line working) in the morning following sleep deprivation. This form of therapy is the most rapid antidepressant treatment in current practice (21). Compared to standard antidepressant treatment, which requires two – eight weeks for improving symptomatology, sleep deprivation therapy is effective within a matter of hours. Light therapy takes a little more time: one – three weeks (1, 6, 18), but it is still efficient.

Sleep phase advance is a form of chronotherapy that shifts progressively the sleeping and waking patterns of the patient and it is often associated with antidepressant treatment. After one day and one night of sleep deprivation, the patient starts a sleep from 6 p.m. to 1 a.m. (seven hours), while the following day, from 8 p.m. to 3 a.m. (seven hours) and the last day, from 10 pm to 5 am, in an attempt to regulate the circadian rhythm, almost always impaired in disorders of the depression spectrum (1, 6).

The three forms of chronotherapy can be associated as a triple therapy (6).

Dark therapy

Another form of chronotherapy focuses on exposure to darkness, and it is particularly useful in bipolar disorder, mostly in manic patients. Keeping them in dark rooms has been shown to improve hyperthymic positive symptomatology and to stop rapid cycling (19, 20).

This form of therapy is interesting because of its immediate response, but it is not very practical. Another alternative is currently under investigation – blue-blocking-sunglasses –, to induce „circadian darkness” without impairing the patient’s vision.

Chronobiotics – melatonin

Melatonin, secreted by the pineal gland, rises in serum levels in the evening, thus preparing the body for sleep. If its secretion is impaired, as in depressive spectrum, sleep disturbances occur. Not a sedative *per se*, exogenous administration of melatonin acts as a genuine *zeitgeber*, to synchronize circadian rhythm and induce sleep. Melatonin has not been shown to have notable effects on mood in persons without affective disorders, but it may worsen depressive symptoms (22). A great deal of research exists on this therapy for persons who are blind or visually impaired and suffering from sleep disturbances, since it provides the synchronizing agent that they lack. However, there are limitations in pre-

scribing melatonin in sleep disturbances, considering the limited data on its safety. An exception is two melatonin antagonists, approved by the Food and Drug Administration, Rozerem and Tasimelteon, strictly used for insomnia (23, 24,

25). Unlike them, the melatonin agonist agomelatine – approved in the European Union – has additional antidepressant properties provided by its serotonergic component, besides its role of *zeitgeber* in sleep regulation (19, 26).

CONCLUSIONS

Chronobiology is a revolutionary perspective when it comes to explain affective symptomatology and sleep disturbances. In exchange, chronotherapy is an approach still open to research, which has already started to prove its efficacy; furthermore, it has a great safety profile and minimum side effects. In monotherapy, combined or associated to classic medication, chronotherapies are therapeutic forms worth to consider for the remission of affective disorders and sleep disturbances; there is a close, bidirectional relation between the two therapies.

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